Natco's Prior Art X (1)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24780 A2 — X

(51) International Patent Classification[7]: A61K 9/52, 31/4439

(21) International Application Number: PCT/IN00/00079

(22) International Filing Date: 25 August 2000 (25.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
968/MAS/99 1 October 1999 (01.10.1999) IN

(71) Applicant *(for all designated States except US)*: **NATCO PHARMA LIMITED** [IN/IN]; Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VENKATESWARA RAO, Pavuluri** [IN/IN]; Manager R & D (F), Natco Pharma Limited, Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033 (IN). **KHADGAPATHI, Podili** [IN/IN]; Director - Technical, Natco Pharma Limited, Natco House, Road No. 2, Banjara Hills, Hyderabad 500 033 (IN).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/24780 A2

(54) Title: AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION

(57) Abstract: The present invention relates to an improved pharmaceutical composition, in the form of a soft gel capsule resistant to digestive juice. The composition of the present invention is made up of gelatin and an enteric polymer in the form of free acid or its salts, containing a benzimidazole derivative used in the treatment of duodenal ulcers, solubilised and/or suspended in a liquid or semisolid medium, comprising of a hydrophobic carrier, an alkaline inert reacting material and a surface active agent and/or a solubilising agent. The present invention also relates to a method for preparing the above said pharmaceutical composition.

AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION.

The present invention relates to an improved pharmaceutical composition and a process for its preparation. The present invention particularly relates to an improved pharmaceutical composition, in the form of a soft gel capsule resistant to digestive juice. The composition of the present invention is made up of gelatin and an enteric polymer in the form of free acid or its salt, containing a benzimidazole derivative used in the treatment of duodenal ulcers, solublised and/or suspended in a liquid or semisolid medium, comprising of a hydrophobic carrier, an alkaline inert reacting material and a surface active agent and/or a solublising agent. The present invention also relates to a method for preparing the above said pharmaceutical composition.

Benzimidazole derivatives such as Omeprazole, Lansoprazole Timoprazole and Pantoprazole etc., are known potent proton pump inhibitors with powerful inhibitory action against the secretion of gastric juice (Lancet, Nov. 27, 1982 pages 1223-1224). They are used in the treatment of Zollinzer – Elision syndrome and stress related esophagitis ulceration. The derivatives are well known and are described, for example in EP-A 0005129.

It has been found that these benzimidazole derivatives, and in particular omeprazole, are susceptible to degradation in acid and neutral media. It is known to protect oral dosage forms of such benzimidazole derivatives by providing an enteric coating. In this way, the active material is protected from acidic gastric juices until it reaches the desired site of release, e.g. the small intestine. Because certain enteric coatings themselves can be, or contain, acidic material, it also often is required to protect the benzimidazole derivatives from the acidity of the enteric coating. For example, it is known to formulate the benzimidazole derivatives with an alkaline material before applying the enteric coating. It is also known to provide an intermediate coating between the benzimidazole derivative and the enteric coating. Generally the intermediate coating is selected so as to be substantially water-soluble or water-dispersible.

EP-A-024 7983; US 4,786,505; US 4,853,230 and US 5,385,739 describe oral pharmaceutical preparations containing benzimidazole derivatives that are potent inhibitors of gastric acid secretion, which are composed of a core material in the form of small beads or tablets containing one of the

benzimidazole derivatives, particularly omeprazole, together with an alkaline reacting compound. The core material contains one or more inert reacting sub-coating layers thereon thereby providing a final outer enteric coating. Although the above-described compositions are reasonably stable over an extended period of storage, discoloration of the pellets and / or tablets with reduced gastric resistance and reduction of dissolution rate in alkaline buffers was observed.

Moreover the processes disclosed above are time-consuming and laborious, involving many stages in manufacturing of the composition, consequently increasing the cost of the final composition.

In a German patent DE 32 22 476 a pharmaceutical composition has been described in which a soft gelatin capsule that is resistant to digestive juice, whose wall includes a usual gelatin mass which contains polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate or a vinyl acetate / crotonic acid copolymer and/or an alkali metal salt, ammonia salt or amino salt of the same in their wall, and which released its contents readily in the intestines within the prescribed time. The capsules are further treated on the surface with an aldehyde-coating agent.

With the capsule shell composition described in DE 32 22 476 above, if used as such for manufacturing capsules containing one of the benzimidazole derivatives in a conventional manner, the free acidic groups of the polymer in the shell composition reacts with the benzimidazole derivatives and reduces the efficacy of the product during its storage / shelf life period.

The above said prior art processes also have the following drawbacks: -

Requirement of sophisticated coating equipment and large amounts of organic solvents / alkali salts are employed to dissolve the enteric polymers for coating the fine particles.

The active substance(s), benzimidazole derivatives, needs to be protected by a sub coat from the reacting acidic groups present in the enteric polymers.

The processing time and the number of steps involved are many.

The resulting product, i.e., pellets / beads / tablets, has to be dried to keep moisture content below 1.5% to ensure drug stability during processing and through its shelf storage.

The active substance(s), benzimidazole derivatives, present in the final formulation as solid dispersed in a hydrophilic solid matrix and hence requires some time to dissolve into the surrounding intestinal fluid before being absorbed.

Large quantities of polymer i.e. 15-25% w/w, based on product, need to be applied to achieve desired gastric protection.

The pH of medium used to suspend / solublise the drug needs to be adjusted to alkaline condition i.e. above pH 8.0 to prevent degradation during processing.

The micro environment surrounding the core also contains alkaline material to neutralise the acidic medium that permeates the outer enteric coating during the product transit through stomach.

In case of pellets / beads large surface area needs to be coated with protective polymer sub-coat.

Considering the importance gained for the composition containing benzimidazole derivatives, particularly for the treatment of duodenal ulcers, there is a need for the development of pharmaceutical composition containing said derivatives having stability for an extended period during which period the composition does not get discoloured and / or degraded.

The present invention is directed to the production of soft gelatin capsules in a conventional manner using gelatin mass having an enteric polymer incorporated into it and to incorporate a mixture containing benzimidazole derivative, and an alkaline reacting substance with larger quantities of hydrophobic oily substance or a mixture of such oily substances into the gelatin shell . The resulting capsules being insoluble up to a pH value of 5.5 in aqueous media, but quickly dissolving above a pH of 6.0.

The invention has been developed based on our finding as a result of sustained R & D work, that the incorporation of benzimidazole derivatives, particularly useful for the treatment of duodenal ulcers, along with an alkaline inert reacting material into a hydrophobic oily substance wherein the benzimidazole derivative is in the form of solution or dispersion, results in extended periods of stability during which period the composition does not get discolored and / or degraded.

In other words, the active ingredient in the composition is kept partially in the form of solution and partially in the form of finely divided particles suspended freely in the oily substance which makes the active ingredient readily absorbable the moment the gastric resistant but intestinal soluble gelatin composition is dissolved.

Such a composition will have an advantage over the existing form of the formulation as the available dosage forms for benzimidazole derivatives are having the total amount of active ingredient in the form of solid particles engulfed in a solid matrix of excipients preferably hydrophilic substances, further coated with protective and gastric resistant enteric polymer coatings. It may take some time to dissolve these coats before the benzimidazole derivative is dissolved into the surronding intestinal fluid and gets absorbed.

Accordingly the main objective of the present invention is to provide an improved pharmaceutical composition containing benzimidazole derivatives having enhanced stability during storage.

According to another objective of the present invention there is provided intestine dissoluble soft gel capsule composition comprising gelatin and an enteric polymer in the form of a free acid or its salt and the pharmaceutical composition comprises benzimidazole derivatives, in particular omeprazole, incorporated in an oily base which is stable during shelf storage.

Still another objective of the invention is to provide a pharmaceutical composition comprising benzimidazole derivatives, to be filled into soft gel capsules, which composition reduces degradation of the benzimidazole derivatives during storage / shelf life.

According to still another objective of the invention there is provided a process for preparation of soft gel capsules comprising benzimidazole derivatives that are resistant to the digestive / gastric juice, a gelatin mass and an enteric polymer in the form of a free acid or as its salt.

Accordingly, the present invention provides, an improved pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises a gelatin shell which is resistant to gastric juice and soluble in intestine having an enteric polymer coating in the form of free acid or its salt, the capsule incorporating a composition comprising of benzimidazole derivative, a hydrophobic oily substance or a mixture of such

oily substances, an alkaline inert reacting material, a dispersing agent, a surface active agent and / or a solublising agent; the resulting capsules being insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.,

According to another feature of the present invention, there is provided a process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises forming a gelatin shell which is resistant to gastric juice and soluble in intestine having an enteric polymer coating in the form of free acid or its salt, incorporating into the resultant capsule a composition comprising a benzimidazole derivative, a hydrophobic oily substance or a mixture of such oily substances, such substance(s) being insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.,an alkaline inert reacting material, a dispersing agent, a surface active agent and / or a solublising agent.

The capsules so formed are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

In a preferred embodiment of the invention, the enteric polymer used in the soft gel capsule composition may be selected from among the polymers but not limited to free acid forms of hydroxypropyl methyl cellulose phthalate, alkylmethacrylate and methacrylic acid ester copolymers, polyvinylacetate phthalate and the like or their ammonia or alkali metal salts. The amount of such enteric polymer employed may range from 5.0 – 40.0 percent, preferably 5.0 – 25.0 percent by weight with reference to the dried shell.

The gelatin mass into which the enteric polymer is incorporated is made up of a composition known in the art and contains gelatin, a plasticizer, preservatives, colourants, opacifiers, flavours etc., as required.

In order to carry out faster dissolution of the enteric polymer for preparing the capsule shell composition, the polymer is first dispersed in water, then an aqueous solution of ammonia or alkali metal salt is mixed while stirring. When alkali metal salt is used it may be selected from substances such as sodium hydroxide, potassium hydroxide, bicarbonate sodium, potassium bicarbonate, sodium carbonate, potassium carbonate etc. The quantity of the base materials used is such that it is sufficient to neutralise 60 to 100 percent of the free acid groups present in the selected enteric polymer.

The excess ammonia or alkali has to be removed from the capsule shell composition to avoid decomposition of the ester couplings in enteric polymers. When aqueous ammonia solution is used to prepare polymer solution, the excess ammonia has to be removed before preparing the capsule after mixing with the gelatin mass, by mixing the mass under reduced pressure in warm condition.

When alkali metal salts are used, the excess alkali is to be neutralized by treating the capsules with an acid selected from any of the following ones, hydrochloric acid, sulphric acid, nitric acid, phosphoric acid, mono carboxylic acids such as acetic acid, propionic acid, benzoic acid etc., dicarboxylic acids such as oxalic acid, maleic acid, fumaric acid etc. The acids are used in the form of cold dilute aqueous solutions in the concentration range of 3 to 30% depending on the type of acid used. The acid treatment may be carried out after manufacturing and partial drying of the capsules to avoid deformation and / or leakage of the capsule contents.

According to another feature of the invention the soft gel capsules are optionally treated with a cross-linking agent that reacts with gelatin and makes it insoluble in gastric juice. The cross-linking agent may be selected from among the aldehydes such as formaldehyde, glutaraldehyde, crotonaldehyde 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde or carbodiimides like 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carbodiimide-metho-p-toluene-sulfonate. The treatment may be done by either coating 0.05 to 1.0% w/v of the substance in an alcohol containing aqueous solution on to the soft gel capsule surface or mixing these substances in the gelatin mass before capsule manufacturing.

According to another feature of the invention the pharmaceutical composition containing benzimidazole derivative, known for its potent proton pump inhibition with powerful inhibitory action against the secretion of gastric juice, is prepared by suspending and/or solubilising the benzimidazole derivative in a carrier mixture composed of a hydrophobic oily carrier material, an alkaline inert reacting material and a dispersing agent and/or a surface active agent. surface active agent. The amount of such benzimidazole derivative used is equivalent to one unit dose recommended depending on the benzimidazole derivative incorporated i.e. for omeprazole the amount incorporated into enteric soft gel capsule may range from 10.0 to 60.0mg per capsule, preferably 20.0 to 40.0 mg per capsule.

The hydrophobic oily material may be selected from among the following fats and oils: Fats and oils of vegetable origin such as sesame oil, corn, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil etc.; animal oils such as fish oil, pig oil, beef oil etc.; esters of straight chained aliphatic oils contained in glycerol such as Sunsoft 700 P-2 (a monoester substance manufactured by Taiho Chemicals Company) Panasete 810 (a triester substance, manufactured by Nippon Oils and Fats); hydrogenated vegetable oils or a mixture thereof. The amount of such hydrophobic oily material may range from 50.0 to 80.0 percent by weight with reference to the contents filled in a capsule.

The alkaline buffering material present in the pharmaceutical composition may be selected from among but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine etc. The amount of such alkaline buffering material present in the composition may range from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight with reference to the contents filled in capsule.

The substances that increase viscosity of the oily material either by dissolving or by forming a colloidal dispersion are used as dispersing agents. The dispersing agent is selected from among but not restricted to colloidal silicon dioxide, polyvinylpyrrolidone etc. The mount of such suspending agent present in the composition may range from 0.5 to 20.0 percent preferably 1.0 to 10.0 percent by weight with reference to the content filled in capsules.

The surface active agent used as solublising and / or dispersing agents is selected from among but is not restricted to substances such as glyceryl monostearate, polyoxyethylene castor oil derivatives such as Cremophor RH 40, Cremophor EL (Make : BASF Corporation), lecithin, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, doccusate sodium etc. The amount of such surface active agent present in the composition may range from 2.0 to 20.0 percent preferably 5.0 to 15.0 percent by weight with reference to contents filled in capsule.

The seamless soft gel capsules can be manufactured on a rotary die machine filling with the liquid and / or semi solid composition containing benzimidazole derivatives.

The invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLE – 1

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methylcellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0
Omeprazole	20.0
Meglumine	20.0
Lecithin	30.0

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule;

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 2

a) **Composition of the Soft gelatin shell:**

Name of the ingredient	Percent by wt.
Gelatin	30.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Ammonia solution (25%w/v)	25.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) **Composition of the medicament :**

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) **Manufacturing of capsule:**

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 3

a) **Composition of the Soft gelatin shell:**

Name of the ingredient	Percent by wt.
Gelatin	40.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	5.0
Ammonia solution (25%w/v)	17.5

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) **Composition of the medicament:**

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) **Manufacturing of capsule:**

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 4

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	25.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	15.0

Gelatin mass containing hydroxypropyl methyl cellulose is prepared by dispersing hydroxypropyl methyl cellulose phthalate in the form of a fine powder in a mixture of glycerin and water maintained at 70°C in which gelatin is dispersed to dissolve forming the gelatin mass. After cooling the mass to 45°C, ammonia solution is added slowly along the stirrer rod while stirring into the gelatin preparation tank. Stirring is continued till hydroxypropyl methyl cellulose phthalate is completely dissolved. The mass is made bubble free by applying vacuum while maintaining the mass at 45 - 50°C under continuous mixing.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Cremohor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in soybean oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed in to the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 5

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Sodium hydroxide solution 1% w/v	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to sodium hydroxide solution at room temperature. Hydroxypropyl methyl cellulose phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Hydrogenated vegetable oil	85.0mg
Lecithin	20.0mg
Pantoprazole Sodium	45.0mg
Meglumine	20.0mg

Hydrogenated vegetable oil is melted and dispersed into soybean oil at 30 - 40°C followed by lecithin, meglumine and pantoprazole sodium and cooled to room temperature. The mixture is kneaded into a smooth paste using a triple roller mill.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 6

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Propylene glycol	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0

Gelatin mass is prepared by dispersing in water at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved in propylene glycol at 60 - 70°C. and mixed with the gelatin mass to obtain uniform mixture.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 7

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Polyvinylacetate phthalate (PVAP)	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Polyvinylacetate phthalate is dissolved by stirring into ammonia solution at room temperature. Polyvinylacetate phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Sunflower oil	200.0mg
Cremophor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in sunflower oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed into the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of a rotary die capsulation machine for manufacture of a capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by a rotary die process.

EXAMPLE – 8

a) **Composition of the Soft gelatin shell:**

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerine	10.0
Triethyl citrate	7.5
Water	20.0
Methacrylic acid co-polymer Type - C	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water triethyl citrate and glycerin maintained at 70°C. Methacrylic acid co-polymer Type - C is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) **Composition of the medicament:**

Name of the ingredient	mg / Capsule
Soybean oil	280.0
Omeprazole	20.0
Meglumine	20.0
Colloidal silicon dioxide	6.0

Colloidal silicon dioxide is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) **Manufacturing of capsule;**

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 9

a) **Composition of the Soft gelatin shell:**

Name of the ingredient	Percent by wt.
Gelatin	30.0
Glycerin	15.0
Water	20.0
Polyvinyl acetate phthalate	10.0
Ammonia solution (25%w/v)	25.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Polyvinyl acetate phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) **Composition of the medicament :**

Name of the ingredient	mg / Capsule
Sun flower oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into Sun flower oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) **Manufacturing of capsule:**

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 10

a) **Composition of the Soft gelatin shell:**

Name of the ingredient	Percent by wt.
Gelatin	40.0
Triethyl citrate	7.5
Glycerin	10.0
Water	20.0
Methacrylic acid co-polymer Type - A	7.5
Ammonia solution (25%w/v)	17.5

Gelatin mass is prepared by dispersing gelatin in a mixture of water Triethyl citrate and glycerin maintained at 70°C. Methacrylic acid co-polymer Type - A is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) **Composition of the medicament:**

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Colloidal silicon dioxide	30.0mg

Colloidal silicon dioxide is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) **Manufacturing of capsule:**

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

The advantages of the present invention are:

1) Simple method of manufacturing, when compared to the methods disclosed in the prior art making the process economical.

2) Improved bioavailability when compared to the solid enteric coated pellets and tablets as the medicament is solublised or suspended in the form of very fine particles in the liquid / semisolid pharmaceutical composition filled into the soft gel capsule.

3) The reactive acidic groups of enteric polymers are in minimal contact with the active ingredient as the polymer is mixed into large amount of gelatin mass. Only small amounts of alkaline reactive material is required to neutralize the free fatty acids in the oily substances and free acidic reacting groups of enteric polymer in contact with the active ingredient on inner surface of the shell.

4) The soft gel does not require any protective sub-coating. Consequently the active ingredient quickly dissolves into the intestinal fluid once the gastric resistant but intestinal soluble gelatin composition is dissolved.

5) The soft gel capsules are simple in composition and therefore do not require any sophisticated equipment for manufacturing.

We claim:

1. A pharmaceutical composition in form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises of a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer mixed into gelatin in the form of free acid or its salt and the capsule incorporating a composition comprising of benzimidazole derivative, a hydrophobic oily substance or a mixture of such oily substances, an alkaline inert reacting material, a suspending agent, a surface active agent and / or a solublising agent; wherein the capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.

2. A pharmaceutical composition as claimed in claim 1 wherein the benzimidazole derivative, is selected from medicaments such as omeprazole, lansoprazole, pantoprazole, timoprazole and the like and the amount present in the formulation is equivalent to one unit dose of selected benzimidazole derivative.

3. A pharmaceutical composition as claimed in claims 1 & 2 wherein the enteric polymer employed for coating the gelatin shell is selected from polymers such as hydroxypropyl methyl cellulose phthalate, alkyl methacrylate and methacrylic acid copolymers, polyvinyl acetate phthalate and the like in the form of free acid or their ammonia or alkali metal salts and the amount employed ranging from 5.0 to 40.0 percent, preferably 5.0 to 25.0 percent by weight, with reference to the dried shell.

4. A pharmaceutical composition as claimed in claims 1 to 3 wherein the benzimidazole derivative in the formulation is suspended / solubilised in a hydrophobic oily substance selected from fats and oils of vegetable origin such as sesame oil, corn oil, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil and the like; animal origin such as fish oil, pig oil, beef oil and the like; esters of straight chain aliphatic oils such as Sunsoft 700 P-2 (Taiho chemical company) Panasete 810 (Nippon oils and Fats); hydrogenated vegetable oils or a mixture thereof and the amount of hydrophobic oily substance used ranging from 50.0 to 80.0 percent by weight, with reference to the contents filled in capsules.

5. A pharmaceutical composition as claimed in claims 1 to 4 wherein substances such ascolloidal silicon dioxide, polyvinylpyrrolidone are used as dispersing agents in an amount ranging from 0.5 to 20.0 percent preferably 1.0 to 10.0 percent by weight and materials such as glyceryl monostearate, lecithin, polyoxyethylene castor oil derivative such as Cremophor RH 40, Cremophor EL (BASF) polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, docusate sodium and the like are used as surface active agent and / or a solublising agent and the amount of surface active agent and/or solublising agent ranging from 2.0 to 20.0 percent, preferably 5.0 to 15.0 percent by weight, with reference to the contents filled in capsule.

6. A pharmaceutical composition as claimed in claims 1 to 5 wherein materials such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine and the like are used as alkaline inert reacting materials and the amount ranging from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight, with reference to the contents filled in capsule.

7. A pharmaceutical composition as claimed in claims 1 to 6 wherein the soft gel capsules are treated with a gelatin cross linking agent such as formaldehyde, glutaraldehyde, crotonaldehyde, 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde; carboimides such as 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carboimide-metho-P-toluene-sulfonate and the like.

8. A pharmaceutical composition as claimed in claims 1 to 7 wherein the soft gel capsules are treated with cold dilute solutions of acids selected from hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, citric acid, propionic acid, benzoic acid, oxalic acid, maleic acid, fumaric acid and the like.

9. A process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/IN 00/00079

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/52 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LEE, SEUNG-JIN ET AL: "Omeprazole enteric-coated soft capsules" retrieved from STN Database accession no. 133:242640 CA XP002164221	10
Y	abstract & KR 131 375 B (S. KOREA) 17 April 1998 (1998-04-17)	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2001	15/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/IN 00/00079

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 32 22 476 A (WARNER LAMBERT CO) 15 December 1983 (1983-12-15) cited in the application page 6, line 20 -page 8, line 27 page 10, line 28 - line 36 examples claims 1-3	1-10
X	WO 98 50019 A (CHEN JIVN REN ;SAGE PHARMACEUTICALS INC (US)) 12 November 1998 (1998-11-12) examples 1,3,5 claims 1,5,6,8	10
P,X	EP 0 960 620 A (RANBAXY LAB LTD) 1 December 1999 (1999-12-01) examples	10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ɔnal Application No
PCT/IN 00/00079

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 131375 B	17-04-1998	NONE	
DE 3222476 A	15-12-1983	NONE	
WO 9850019 A	12-11-1998	AU 7375598 A	27-11-1998
EP 0960620 A	01-12-1999	AU 1979699 A	13-12-1999
		CN 1237415 A	08-12-1999
		WO 9961022 A	02-12-1999